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Hydrocarboxylation of unactivated internal alkynes with carboxylic acids catalyzed by dinuclear palladium complexes

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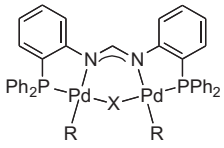
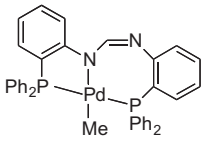
ABSTRACT

Dinuclear palladium complexes catalyzed addition reactions of carboxylic acid O–H bond to unactivated internal alkynes. The reaction afforded a *trans*-adduct selectively.

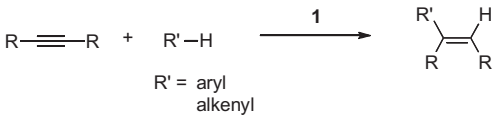
Dinuclear transition metal complexes have been expected to have novel and unique functions as catalysts in organic synthesis.[1] The co-operation of two metal centers could enable various transformations that are not possible using mononuclear metal complexes. We have previously reported that dinuclear palladium complexes with a novel bridging ligand, *N,N′*-bis[2-(diphenylphosphino)phenyl]amidinate[2] (dpfam), served as catalysts for selective addition reactions of various sp^2 and sp C–H bonds to unactivated alkynes,[3] which were not possible using mononuclear palladium complexes (Eq. 1). In the course of our study for the catalysis using **1**, we found that the addition of carboxylic acid O–H bond to unactivated internal alkynes proceeded in the presence of **1a** (Eq. 2). Hydrocarboxylation of alkynes with carboxylic acids is an atom economical way to synthesize vinyl and alkenyl esters, some of which are industrially important compounds.[4] Although there have been many reports concerning hydrocarboxylation catalyzed by transition metals,[4,5] *intermolecular* addition to *internal* alkynes has been rather limited.[6] Hidai and co-workers reported that a cuboidal palladium–molybdenum cluster served as a catalyst for addition to electron-deficient internal alkynes as well as terminal alkynes.[6a] Unactivated internal alkynes react with several carboxylic acids in the presence of silver salts.[6b] $Ru_3(CO)_{12}$ is also effective for the hydrocarboxylation of unactivated alkynes to afford (*Z*)-alkenyl esters.[6c–e]





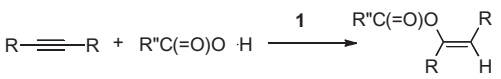
1a (X = OH, R = *p*-Tol)
1b (X = OH, R = Me)
1c (X = I, R = *p*-Tol)
1d (X = Br, R = *p*-Tol)
1e (X = Cl, R = *p*-Tol)

2



R' = aryl
alkenyl
alkynyl

(1)



(2)

Initially, the reaction of 3-hexyne with benzoic acid was carried out under reaction conditions similar to that of the hydroarylation[3a] of internal alkynes using **1** (Eq. 3 and Table 1). Reactions in the presence of **1** and tri-*n*-butylborane at 100 °C afforded *Z*-1-ethylbut-1-enyl benzoate **3**[7] as the sole product. No regio- and stereoisomers were observed. Hydroxo-bridged complexes **1a** and **1b** were more effective than halide-bridged complexes **1c–e**. Reaction using **1a** or **1b** as a catalyst afforded **3** in good yields

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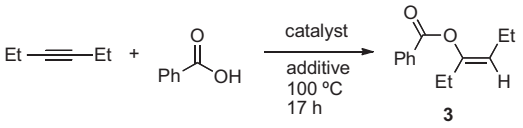
Table 1
Pd-catalyzed addition of benzoic acid to 3-hexyne[a]

Run	Catalyst (mol %)	Additive	Yield[b] (%)
1	**1a** (2)	B(*n*-Bu)$_3$	71
2	**1b** (2)	B(*n*-Bu)$_3$	65
3	**1c** (2)	B(*n*-Bu)$_3$	27
4	**1d** (2)	B(*n*-Bu)$_3$	44
5	**1e** (2)	B(*n*-Bu)$_3$	41
6	**1a** (2)	None	53
7	**1a** (2)	B(*sec*-Bu)$_3$	55
8	**1a** (2)	LiAl(O-*t*-Bu)$_3$H	51
9	**2** (4)	B(*n*-Bu)$_3$	4
10	Pd(PPh$_3$)$_4$ (4)	B(*n*-Bu)$_3$	0
11	Pd(OAc)$_2$ (4)	B(*n*-Bu)$_3$	0
12	None	B(*n*-Bu)$_3$	0

[a] A mixture of 3-hexyne (0.5 mmol) and benzoic acid (5.0 mmol) was stirred at 100 °C for 17 h in the presence of a palladium complex (0.01–0.02 mmol) and an additive (0.15 mmol).
[b] Determined by GC.

(entries 1 and 2). Although **1c**–**e** were wholly ineffective in the previous hydroarylation,[3a] hydrocarboxylation proceeded in the presence of **1c**–**e** to give **3** in moderate yields (entries 3–5). The addition of tri-*n*-butylborane is not essential for hydrocarboxylation in contrast to hydroarylation; however, the absence of the additive decreased the yield of **3** (entry 6). The addition of tri-*sec*-butylborane or lithium tri-*tert*-butoxyaluminum hydride did not affect the yield of **3** (entries 7 and 8). Next, several mononuclear complexes were employed as catalysts. The reaction did not proceed in the presence of ordinary palladium catalysts such as Pd(PPh$_3$)$_4$ and Pd(OAc)$_2$ (entries 10 and 11). Only the mononuclear complex **2**, which has the same ligand as the dinuclear complexes **1** have, showed very low catalytic activity (entry 9).



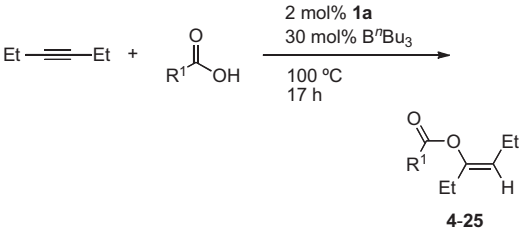
(3)

Table 2
Pd-catalyzed addition of various carboxylic acids to 3-hexyne[a]

Run	R^1	Product	Yield[b] (%)
1	*o*-MeC$_6$H$_4$	**4**	58
2	*o*-MeOC$_6$H$_4$	**5**	40[c]
3	*o*-CF$_3$C$_6$H$_4$	**6**	88
4	*o*-FC$_6$H$_4$	**7**	62
5	*o*-CH$_3$(C=O)C$_6$H$_4$	**8**	Trace
6	*m*-MeC$_6$H$_4$	**9**	24
7	*m*-MeOC$_6$H$_4$	**10**	41
8	*m*-CF$_3$C$_6$H$_4$	**11**	32[d]
9	*p*-CH$_3$C$_6$H$_4$	**12**	Trace
10	2-Pyrroryl	**13**	0
11	2-Pyridyl	**14**	0
12	2-Furyl	**15**	57
13	2-Thienyl	**16**	50
14	*trans*-PhCH=CH	**17**	74
15	*trans*-PrCH=CH	**18**	42
16	*trans*-MeCH=CH	**19**	29
17	Me	**20**	20
18	Et	**21**	23
19	ClCH$_2$	**22**	23
20	Cyclohexyl	**23**	42
21	PhCH$_2$	**24**	47
22	PhCH$_2$CH$_2$	**25**	66

[a] A mixture of 3-hexyne (0.5 mmol) and a carboxylic acid (5.0 mmol) was stirred at 100 °C for 17 h in the presence of **1a** (0.01 mmol) and B(*n*-Bu)$_3$ (0.15 mmol, 1 M THF solution).
[b] Isolated yields.
[c] *E*/*Z* = 14/86.
[d] *E*/*Z* = 24/76.

Table 2 summarizes the results of the reaction of 3-hexyne with various carboxylic acids (Eq. 4). Most reactions with substituted benzoic acids also gave the corresponding alkenyl esters **4**–**12** (entries 1–9). While electron-donating groups slightly decrease the yield of the products, electron-withdrawing groups increase the yield (entries 1–4). An acetyl group at the *ortho* position inhibits the reaction, probably due to deactivation of the catalyst by chelation (entry 5). In several cases, small amounts of isomers were observed by GC–MS. The structure of the isomers was determined by ^{1}H NMR spectra only in two reactions where significant amounts of isomers were formed (entries 2 and 8). The standard reaction conditions are unsuitable for the reaction with *p*-toluic acids (entry 9). In this case, the reaction mixture was heterogeneous because only a small amount of THF was used as the solvent and *p*-toluic acid has lower solubility and a higher melting point. Although nitrogenous heteroaromatic carboxylic acids such as 2-picolinic acid and pyrrole-2-carboxylic acid inhibited the addition (entries 10 and 11), the reaction of 2-furoic acid or 2-thiophenecarboxylic acid gave the corresponding adducts **15** and **16**, respectively (entries 12 and 13). Alkenoic acids can also be used for hydrocarboxylation (entries 14–16); the reaction of cinnamic acid afforded the adduct **17** in a satisfactory yield. Most aliphatic carboxylic acids exhibited low reactivity. Among them, phenyl-substituted acids, such as phenylacetic acid and hydrocinnamic acid were more reactive and adducts **24** and **25** were obtained from their reactions (entries 21 and 22).



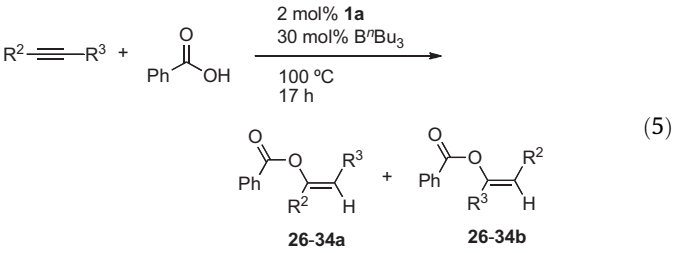
(4)

Table 3 summarizes the results of the reaction of various alkynes with benzoic acid (Eq. 5). Various dialkylethynes reacted with benzoic acid as well as 3-hexyne to provide the corresponding esters **26**–**29** (entries 1–4). Unfortunately, a hindered group inhibited the reaction (entry 3) and the regioselectivity in the reaction of 2-octyne was low (entry 4). The regioselectivity increased slightly in the reactions of phenyl-substituted alkynes (entries 6 and 7), and was significantly improved in the reaction of methyl butynoate, although the *E*/*Z* ratio was low (entry 9). Terminal alkynes such as phenylacetylene and 1-hexyne afforded no adducts.

Table 3
Pd-catalyzed addition of benzoic acid to various alkynes[a]

Entry	R^2	R^3	Product	Yield[b] (%)	**a**:**b**
1	*n*-Pr	*n*-Pr	**26**	29	—
2	*n*-Bu	*n*-Bu	**27**	32	—
3	Me	*t*-Bu	**28**	0	—
4	Me	*n*-C$_5$H$_{11}$	**29**	58	51:49
5	Ph	Ph	**30**	15	—
6	Me	Ph	**31**	55	65:35
7	Et	Ph	**32**	36[c]	69:31
8	CO$_2$Me	CO$_2$Me	**33**	41[d]	—
9	Me	CO$_2$Me	**34**	70[e]	100:0

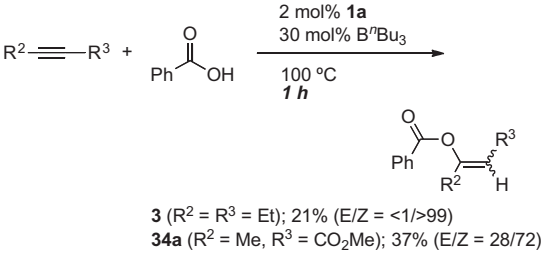
[a] A mixture of an alkyne (0.5 mmol) and benzoic acid (5.0 mmol) was stirred at 100 °C for 17 h in the presence of **1a** (0.01 mmol) and B(*n*-Bu)$_3$ (0.15 mmol, 1 M THF solution).
[b] Isolated yields.
[c] *E*/*Z* = 16/84 (**32a**), 26/74 (**32b**).
[d] *E*/*Z* = 50/50.
[e] *E*/*Z* = 29/71.



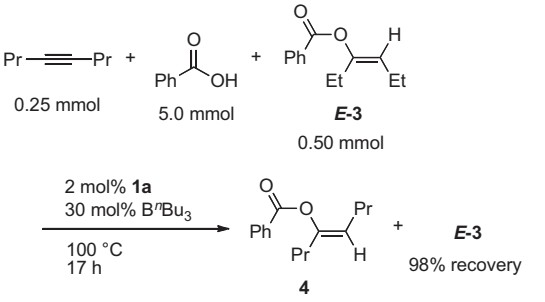
(5)

While hydroarylation did not proceed without trialkylboranes,[3a] those are not essential for hydrocarboxylation. As indicated previously, trialkylboranes could serve as a hydride source to transform a hydroxo-bridged complex into a hydride-bridged complex, which could be a true reaction intermediate.[3a] Actually, lithium tri-*tert*-butoxyaluminum hydride can be used instead of trialkylboranes.[3b] An acidic hydrogen atom of benzoic acid would be a hydride source for generation of a hydride-bridged complex.[8] Therefore hydrocarboxylation does not need additives essentially.

Hydroarylation,[3a,b] hydroalkenylation[3c] and hydroalkynylation[3d] catalyzed by **1** proceeded selectively via *cis*-addition, whereas the present hydrocarboxylation afforded mainly *trans*-adducts. To elucidate whether the *trans*-adducts were generated by the isomerization of *cis*-adducts, the *E*/*Z* ratio of products was observed at the early stage of several reactions. After 1 h, the reaction of 3-hexyne with benzoic acid gave only the *trans*-adduct **Z-3** in low yield and with high stereoselectivity (Eq. 6). The *E*/*Z* ratio of **34** in the 1-h reaction of methyl butynoate was 29/71, which was similar to that after 17 h (Table 3, entry 9). Next, the pure *E*-isomer of **3**, which was prepared by a different method,[6d] was added to the reaction of 4-octyne with benzoic acid (Eq. 7). After 17 h, no isomerization of **E-3** to **Z-3** was observed. These results show that the *trans*-adducts are not generated by isomerization of the *cis*-adducts.

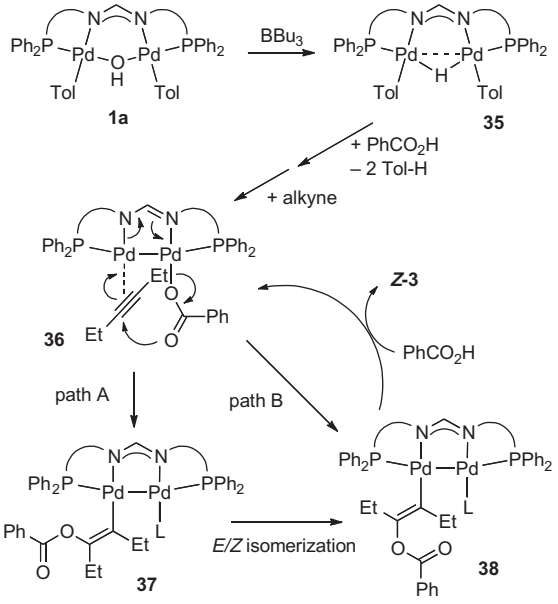


(6)



(7)

Although there is little evidence for the mechanistic aspects at the present time, one of the possible mechanisms for the reaction of 3-hexyne with benzoic acid is described in Scheme 1.[3e] As mentioned above, the reaction of **1a** with tri-*n*-butylborane could give hydride-bridged complex **35**. Reductive elimination of toluene from **35**, followed by protonation of another tolyl ligand with benzoic acid, would afford benzoate complex **36**. Insertion of 3-hexyne into Pd–Pd bond[9] of **36** and reductive elimination on the right palladium center could result in *cis*-addition to give alkenyl palladium complex **37** (path A). Complex **38** could be generated via *E*/*Z* isomerization of the alkenyl ligand,[10] and protonated with benzoic acid to afford **Z-3**. Nucleophilic attack of benzoate to alkyne from the opposite side of palladium in **36** could also generate complex **38** directly (path B).



Scheme 1. Possible mechanisms.

In summary, the dinuclear palladium complex **1** catalyzed the hydrocarboxylation of internal alkynes with carboxylic acids to predominantly yield *trans*-adducts. The precise reaction mechanism and addition reactions of other O–H bonds to alkynes are under investigation.

Supplementary data

Supplementary data (experimental details and product characterizations) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.046.

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